Evaluating Risk in Older Adults Using Physiologically Based Pharmacokinetic Models

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The rapid growth in the number of older Americans has many implications for public health, including the need to better understand the risks posed by environmental exposures to older adults. An important element for evaluating risk is the understanding of the doses of environmental toxicants that reach potential target organs and how long these toxicants dwell in the body. While some data exist on the responses of older adults to therapeutic medications, there are broad data gaps in our understanding of the determinants of dosimetry to toxicants in this subpopulation. Researchers in the ORD's National Health and Environmental Effects Research Laboratory (NHEERL) and National Exposure Research Laboratory (NERL) are collaborating with the EOHSI, a joint project of UMDNJ and the R.W. Johnson Medical School and Rutgers University, to produce physiologically based pharmacokinetic (PBPK) models that mathematically describe the physiology of older individuals in the context of chemical absorption, distribution, metabolism, and excretion (ADME). The ORD researchers have extensive experience in developing and applying PBPK models toward human health risk assessment; the EOHSI brings advanced computational methods required to determine which changes in model parameters most affect tissue dosimetry and toxicity for prototype toxicants. The representation of the physiological and biochemical pathways with these models allows for the evaluation of changes to the risk metrics as the effects of aging are implemented in the model. These effects may include decline in renal function, changes in tissue composition, and changes to metabolic enzymes due to age, health status, or medications. PBPK models will be developed for a diverse set of chemicals relevant to the diverse population of older adults. This research will identify characteristics that are associated with enhanced risk in older adults. These results will be used to predict who in the older adult subpopulation may be most susceptible and which toxicants present the greatest risks based on known changes in pharmacokinetics with age, disease, pharmaceutical use, and diet. This work will also help to identify areas on which future research should be focused to efficiently reduce uncertainties in risk assessment.

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